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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: MUKAI=1

In re Application of:) Art Unit: 1645
Hiroyuki MUKAI et al) Examiner:
Appln. No.: 09/935,338) Washington, D.C.
Date Filed: August 23, 2001) Confirmation No. 815
For: METHOD FOR AMPLIFYING) July 15, 2002
NUCLEIC ACID SEQUENCE

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**PETITION FOR ACCELERATED EXAMINATION UNDER
MPEP 708.02, PART VII, SPECIAL EXAMINING PROCEDURE
FOR CERTAIN NEW APPLICATIONS**

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby petition for accelerated examination of the above-identified application under Part VII of MPEP 708.02, which requires the five elements set forth below:

A) Please consider the present paper to constitute a Petition To Make Special. The required fee in the amount of \$130.00 as required by 37 CFR 1.17(i) is attached hereto.

B) If the PTO determines that all the claims presented are not obviously directed to a single invention, applicants agree to make an election without traverse.

Applicants wish to proceed with claims directed to an amplification method, the main claim of which is claim 221, including claims 221-241, 243-252 and 263-268; and claims directed to a detection method, namely claims 272-275, which are directed to amplifying a target nucleic acid by the amplification method.

If a restriction requirement is imposed, applicants authorize deletion of the non-elected claims without prejudice to the elected subject matter and without prejudice to applicants' rights, including those rights provided by §§121, 120 and 119, to proceed with one or more divisional application without any penalty whatsoever.

C) Applicants are required to submit a statement that a pre-examination search was made, and a search made by a foreign patent office satisfies this requirement.

In this regard, an international search was conducted which satisfies this requirement. The documents cited in the international search report were incorporated in an Information Disclosure Statement (IDS) filed in the present application on October 23, 2001, along with a copy of the International Search Report which can serve as a foreign pre-examination search statement. These documents are also listed below:

Reference 1: WO 99-09211 A

Reference 2: US 5,824,517 A

Reference 3: US 5,648211 and US 5,744,311
(equivalent of JP 7-289298 A)

D) Applicants are required to submit one copy of each of the references deemed most closely related to the subject matter encompassed by the claims, if such references are not already of record. Such documents are already of record, having been presented in the aforementioned IDS. However, a duplicate copy of each is submitted herewith.

E) Applicants are required to submit a detailed discussion of the references pointing out, with the particularity required by 37 CFR 1.111(b) and (c) how the claimed invention is patentable over each of the references. This detailed discussion appears immediately below:

WO 99-09211 A (Cited Reference 1)

Claim 1 of Cited Reference 1 reads as follows:

1. A method of amplifying a nucleic acid sequence present in a first strand of a double stranded nucleic molecule comprised of complementary first and second strands wherein said molecule incorporates an unmodified recognition site for a restriction enzyme capable of

cutting the first strand at the 5' end of the sequence therein to be amplified and leaving the 3'-end region of the second strand projecting beyond the cut site in the first strand, and said method comprises

treating said nucleic acid molecule with said enzyme in the presence of a strand displacing polymerase and unmodified nucleotides for incorporation in extending nucleic acid strand under conditions such that there is or becomes hybridized to said 3'-end region of the second strand a primer sequence complementary thereto whereby said primer sequence is extended in the 5' to 3' direction using the second strand as a template to re-generate the restriction endonuclease cut site and displace the sequence to be amplified.

A restriction enzyme capable of cutting the first strand at the 5' end of the sequence therein to be amplified and leaving the 3'-end region of the second strand projecting beyond the cut site in the first strand (i.e. a restriction enzyme that produces a 3'-overhang) is used in the method of Cited Reference 1. Using such a restriction enzyme, a first strand of a double stranded nucleic acid molecule comprised of complementary first and second strand is cut at a

recognition/cut site for the restriction enzyme present at the 5' end of the nucleic acid sequence to be amplified. Then, there is or becomes hybridized to said 3'-end region of the second strand (which has been made single-stranded as a result of the cutting) a primer sequence complementary thereto whereby said primer sequence is extended in the 5' to 3' direction using the second strand as a template to re-generate the restriction endonuclease cut site and displace the sequence to be amplified. Consequently, the nucleic acid sequence is amplified. Thus, the method of Cited Reference 1 requires use of a restriction enzyme that produces a 3'-overhang and presence of a recognition/cut site for the restriction enzyme in the nucleic acid molecule containing the nucleic acid sequence to be amplified (see, for example, Fig. 2 and Fig. 3 of Cited Reference 1).

It is nearly impossible to expect that a recognition/cut site for a restriction enzyme that produces a 3'-overhang sufficient for hybridization with a primer inherently exists adjacent to a sequence to be amplified. As a restriction enzyme to be used, only TspRI which produces a 9-base 3' overhang is disclosed in Cited Reference 1. Since the sequence selected for the primer used in the method of Cited Reference 1 depends on the recognition/cut site for the restriction enzyme, it is difficult at the least, if not

impossible, to select a sequence for the primer optimal for amplification of the target nucleic acid. In addition, if such a site is absent, it is necessary to artificially introduce a recognition/cut site for the restriction enzyme using an additional primer (called ISOS primer) (see page 4, lines 4 to 19 of Cited Reference 1).

The method of the claimed invention does not require use of a restriction enzyme or presence of a recognition/cut site for the restriction enzyme in a nucleic acid as a template. Thus, the claimed invention is non-obviously different from the subject matter contained in Cited Reference 1. Furthermore, Cited Reference 1 does not teach or suggest an endonuclease or a chimeric oligonucleotide primer used in the claimed invention.

US 5,824,517 (cited Reference 2)

Claim 1 of Cited Reference 2 reads as follows:

1. A method for amplifying a target nucleic acid sequence, said sequence comprising, starting from its 5' end, an upstream region, and, starting from its 3' end, a downstream region,

said method comprising the steps of:
obtaining a DNA-type single stranded polynucleotide comprising a first segment

corresponding to the target sequence to be amplified and at least a second segment of arbitrary sequence located downstream of the 3' end of said first segment; and

placing said single-stranded polynucleotide in contact with an excess amount of a set of primers, in the presence of an enzyme system with DNA-dependent DNA polymerase activity, strand displacement activity, and RNase H activity, and in the presence of an excess amount of deoxyribonucleotide triphosphates such that said target nucleic acid sequence is amplified, said set of primers comprising at least one primer selected from the group consisting of:

- 1) a first chimeric primer comprising successively, in the 5'→3' direction: an RNA-type segment with a sequence complementary to at least a portion of said second segment of said single-stranded polynucleotide, said portion comprising at least the 5' end of said second segment , and a DNA-type segment capable of hybridizing with at least a portion of said downstream region, said portion comprising at least the 3' end of said downstream region, and
- 2) a second chimeric primer comprising successively, in the 5'→3' direction: and RNA-type

segment of arbitrary sequence, and a DNA-type segment homologous with at least a portion of said upstream region, said portion comprising the 5' end of said upstream region,

wherein:

either the first primer further comprises, upstream of the RNA-type segment, a second DNA-type segment of arbitrary sequence having a 3' end capable of hybridizing with the 3' end of said polynucleotide when said RNA segment is shorter than said second segment of said single-stranded polynucleotide,

or the first primer does not comprise such a second DNA-type segment, then said set of primers further comprises a third primer comprising a 3' end capable of hybridizing with at least a portion of said second segment of said single-stranded polynucleotide,

and wherein:

either the second primer further comprising, upstream of the RNA-type segment, a second DNA-type segment of arbitrary sequence,

or the second primer does not comprise such a second DNA-type segment, then said set of primers further comprises a fourth primer comprising a 3' end

that is homologous with at least a portion of the sequence of the RNA-type segment of the second primer.

See, for example, Figure 5 of Cited Reference 2.

The method for amplifying a target nucleic acid sequence of Cited Reference 2 comprises a step of obtaining a DNA-type single-stranded polynucleotide comprising a first segment of arbitrary sequence located downstream of the 3' end of said first segment. Specifically, a DNA-type single stranded polynucleotide comprising a target sequence defined by an upstream region and a downstream region (a first segment) and an additional arbitrary sequence (a second segment) as a template is subjected to an amplification step in the method of Cited Reference 2.

Regarding the arbitrary sequence, Cited Reference 2 describes the following: in one particular embodiment, in order to limit the number of nucleotide primers used, the first and second chimeric primers may be chosen to be identical or partially identical. In particular, their respective RNA-type segments can be identical. Likewise, their second (optional) DNA-type segments may be identical if they are present. Moreover, the third and fourth primers may be identical and may in particular be homologs of the RNA-type segment of the first and/or second primers (column 7, line 63 to column 8, line 5 of Cited Reference 2). For example,

according to the aspect defined by claim 7 of Cited Reference 2, up to six primers can be advantageously reduced by the addition of an identical sequence for the arbitrary sequences.

On the hand, the chimeric oligonucleotide primer used in the method of the instant invention is substantially complementary to the nucleotide sequence of the nucleic acid as the template. There is no need to add "an arbitrary sequence" to the nucleic acid as the template. Thus, the presently claimed invention is non-obviously different from the subject matter contained in Cited Reference 2. Furthermore Cited Reference 2 does not teach or suggest a chimeric oligonucleotide primer that is substantially complementary to the nucleotide sequence of the nucleic acid as the template used in the claimed invention.

US 5,648,211 A & US 5,744,311 (Cited References 3 and 4)

Since the disclosure of Cited Reference 4 is similar to that of Cited Reference 3, only Cited Reference 3 is discussed below. Claim 1 of Cited Reference 3 is as follows:

1. A method for amplifying a target sequence comprising:

A) providing a single stranded nucleic acid fragment containing the target sequence, the fragment having a 5' end and 3' end;

B) binding an amplification primer for SDA to the 3' end of the fragment such that the primer forms a 5' single stranded overhang, the amplification primer comprising a recognition/cleavage site for a thermophilic restriction endonuclease which does not cut the target nucleic acid sequence, and:

C) amplifying the target sequence at 50°C-60°C in a reaction comprising the steps of:

i) extending the amplification primer on the fragment in the presence of

a) a thermophilic DNA polymerase having a temperature optimum for polymerizing activity if 65C-75°C, the polymerase having strand displacing activity and lacking 5'-3' exonuclease activity,

b) deoxynucleoside triphosphates,

c) at least one derivatized deoxynucleoside triphosphate, and

d) a thermophilic restriction endonuclease which nicks the recognition/cleavage site when the site is hemimodified by incorporation of the derivatized deoxynucleoside triphosphate, the endonuclease having a temperature optimum for cleavage of double-stranded DNA of 50°C-65°C,

thereby producing a first double stranded product comprising the amplification primer, a first newly synthesized strand complementary to the target sequence, and a double strand hemimodified restriction endonuclease recognition/cleavage site;

ii) nicking the double stranded hemimodified restriction endonuclease recognition/cleavage site with the restriction endonuclease;

iii) extending from the nick using the DNA polymerase, thereby displacing the first newly synthesized strand from the fragment and generating a second extension product comprising a second newly synthesized strand, and;

iv) repeating the nicking, extending and displacing steps such that the target sequence is amplified.

See, for example, Fig. 1 and Fig. 2 of Cited Reference 3.

As seen from the title of the patent, Cited Reference 3 relates to the Strand Displacement Amplification (SDA) method in which thermophilic enzymes are used. The method of Cited Reference 3 comprises extending an amplification primer comprising a recognition/cleavage site for a restriction endonuclease in the presence of a

derivatized deoxynucleoside triphosphate; nicking a restriction endonuclease recognition/cleavage site hemimodified by incorporation of the derivitized deoxynucleoside triphosphate with the restriction endonuclease; and extending from the nick.

Thus, the method of Cited Reference 3 requires a restriction endonuclease, an amplification primer comprising a recognition/cleavage site for the restriction endonuclease, and derivatized deoxynucleoside triphosphate.

On the other hand, according to the instant invention, it is not required that an amplification primer comprises a recognition/cleavage site for a restriction endonuclease. Furthermore, the presently claimed invention does not require use of a restriction endonuclease or a derivatized deoxynucleoside triphosphate. Thus, the claimed invention is non-obviously different from the subject matter contained in Cited Reference 3. Furthermore, Cited Reference 3 does not teach or suggest an endonuclease or a chimeric oligonucleotide primer used in the claimed invention.

Based on the discussion provided above, applicants submit that it should be clear that applicants' invention is both novel and nonobvious from the cited references.

Applicants respectfully request that accelerated examination be approved and carried out, and applicants respectfully await the results of a first examination on the merits.

Respectfully submitted,

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/01534

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl⁷ C12N15/10, C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl⁷ C12N15/10, C12Q1/68

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI (DIALOG), BIOSIS (DIALOG), JICST FILE (JOIS), DDBJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, 99-9211, A (TEPNEL MEDICAL), 25 February, 1999 (25.02.99) & ZA, 9807257, A " & AU, 9887403, A	1-83
A	US, 5824517, A (Bio Merieux), 20 October, 1998 (20.10.98) & WO, 97-4126, A1 & FR, 2737223, A1 & EP, 787209, A1	1-83
A	JP, 7-289298, A (BECTON DICKINSON AND COMPANY), 07 November, 1995 (07.11.95) & AU, 9514776, A & EP, 684315, A1 & BR, 9501581, A & CA, 2144495, A & SG, 28239, A1 & US, 5648211, A & US, 5744311, A	1-83

Further documents are listed in the continuation of Box C.

See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search
09 June, 2000 (09.06.00)

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20 June, 2000 (20.06.00)

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